



**APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS
INCLUDING NOTATIONS TO INDICATE CHANGES MADE**

Applicant(s): James B. McCarthy et al.

Serial No.: 09/937,076

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For: METHODS OF USE OF β_1 -INTEGRIN INHIBITORS

Amendments to the following are indicated by underlining what has been added and bracketeting what has been deleted. Additionally, all amendments have been shaded.

In the Specification

The paragraph beginning at page 35, line 2, has been amended as follows:

Transient cerebral ischemia and associated brain injury may be mediated by several factors, including inflammatory processes (Hallenbeck et al., Stroke, 17, 246-253 (1986)). Leukocyte infiltration into ischemic tissue is a pathophysiological response, which often further aggravates ischemic injury by attenuating microvascular blood flow, and releasing chemical mediators such as free oxygen radicals (Kochanek et al., Stroke, 23, 1367-1379 (1992); and Matsuo et al., J. Cereb. Blood Flow Met., 15, 941-947 (1995)). Cell adhesion molecules play important roles in leukocyte-endothelial interactions: the selectins (Lasky, Science, 258, 964-969 (1992)), the integrins, and the immunoglobulin superfamilies (Springer, Nature, 346, 425-434 (1990)). Integrins which contain β_1 subunits usually are associated with mediating adhesion to extracellular matrix constituents (Springer, Nature, 346, 425-434 (1990)) whereas β_2 integrins are largely involved in cell-cell interactions. One of these extracellular matrix macromolecules is fibronectin, which is found in plasma, cell matrix, and on the cell surface. These molecules can support leukocyte adhesion to endothelial cells (Akiyama et al., Adv. Enzymol., [57]59, 1-57 (1987)).

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For: METHODS OF USE OF β 1-INTEGRIN INHIBITORS

The paragraph beginning at page 35, line 18, has been amended as follows:

Fibronectin possesses multiple domains recognized by integrins, including arginyl-glycyl-aspartic acid (RGD). The latter interacts selectively with $\alpha 5\beta 1$ integrin, and the alternately spliced connecting segment domain (CS-1) which is recognized selectively by $\alpha 4\beta 1$ integrin (Akiyama et al., Adv. Enzymol., [57]59, 1-57 (1987); and Guan et al., Cell, 60, 53-61 (1990)). Over the last few years several novel (nonRGD/nonCS-1) bioactive peptides from fibronectin that: a) antagonize leukocyte adhesion of activated lymphocytes and monocytes *in vitro* when used as soluble antagonists and b) show efficacy for improved outcomes in several *in vivo* animal models of chronic and acute inflammation when administered intravenously. These models include bacterial cell wall-induced arthritis in rats, models of autoimmune disease such as TGF- β -/- mice, and reperfusion injury in rat transient cerebral ischemia and in rabbit burn models (Hines et al., Proc. Natl. Acad. Sci., USA, 91, 5187-5191 (1994); Wahl et al., J. Clin. Invest., 94, 655-662 (1994); and unpublished data).